

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 31/135		A1	(11) International Publication Number: WO 94/21244 (43) International Publication Date: 29 September 1994 (29.09.94)
(21) International Application Number: PCT/US94/02875 (22) International Filing Date: 17 March 1994 (17.03.94) (30) Priority Data: 034,834 17 March 1993 (17.03.93) US		(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>	
(71)(72) Applicant and Inventor: HITZIG, Pietr [US/US]; 1319 Blue Mount Road, Monkton, MD 21111 (US). (74) Agent: CRAWFORD, Arthur, R.; Nixon & Vanderhye, 8th floor, 1100 North Glebe Road, Arlington, VA 22201-4714 (US).			
(54) Title: METHOD OF TREATING ADDICTIVE BEHAVIORS			
(57) Abstract <p>Treatment of addictive behavior, depression or manic depressive behavior, excluding obesity, is described in which an effective amount of at least one serotonin agonist and at least one dopamine agonist is administered to a patient. The combination of the serotonin agonist and the dopamine agonist are present in an amount effective to treat the patient's addictive behavior. Pharmaceutical compositions are also disclosed.</p>			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Iceland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

METHOD OF TREATING ADDICTIVE BEHAVIORS

Alcohol dependence, one form of addictive behavior, is one of the most preventable and treatable current health problems. Although existing treatments of alcoholism can be effective they are not suited to all patients and often result in abstinence or non-hazardous drinking for a short time. Medications offer one way to improve the treatment of alcoholics. To this end I have devised and hereby disclose a form of therapy that is effective in reducing and often eliminating the craving and use of alcohol as well as other substances of abuse.

BACKGROUND OF THE INVENTION

The addictions of alcohol¹ and food have been and are now under increasing pharmacologic attack. Against alcoholism are arrayed various re-uptake inhibiting serotonin agonists² including fluoxetine,³ and citalopram.⁴ In addition Krasner⁵ and colleagues have studied fenfluramine, a serotonin agonist but not a classical serotonin re-uptake inhibitor. These drugs alone cause significant but modest decreases in alcohol consumption.

Against hyperphagia, the front is even more advanced. Over the last ten years, Hoebel and his associates at Princeton have integrated experiments done elsewhere with their own elegant work. Their model has and will continue to guide many researchers to rewarding areas of experiment. Weintraub and colleagues reported in 1984⁶ and in 1992⁷ that fenfluramine and phentermine together act synergistically against food craving and obesity. They stated that this combination had "capitalized on pharmacodynamic differences, resulting in equivalent weight loss, fewer adverse effects, and better appetite control." This study continued these medications for three years, strongly suggesting obesity could be

managed as a chronic illness without either untoward medication induced side-effects or tachyphylaxis.

Animals trained to self-stimulate themselves with electrodes placed in different areas of the brain have been invaluable in neurophysiologic research. When electrodes are placed in the medial fore-brain bundle, dopamine is released when the animal presses the pedal. The animal is thereby rewarded. Many studies utilizing this procedure as a model for addictive behavior have been performed over the years. A recent study showed that while racemic fenfluramine by itself decreased the rate of self-stimulation, combining fenfluramine with amphetamine was far more effective. These chemicals, administered together, abolished lever pressing for up to three hours.⁸ The authors felt that their findings support a dopamine-serotonin interaction in self-stimulation (addictive), behavior.

There are many similarities between primary obesity and alcoholism. The ingestion of either food or drink increases dopamine and serotonin in the nucleus accumbens (NAC).^{9,10,11,12,13} Craving and loss of control in alcohol abuse and dependency may have a neurophysiologic basis within basal ganglial/limbic striatal and thalamo-cortical neuronal systems. These same dopaminergic systems are involved with neuronal modulation of hunger and satiation.¹⁴ Both cravings are modestly ameliorated by serotonin agonists.

In normal subjects, dopamine and serotonin production decrease from waking to sleep.¹⁵ It is postulated I believe that the non-addicted, or so-called normals, reverse this dual amine decline by consuming their main

meal of the day after sunset.¹⁶ If they wish, alcohol consumption and sexual relations will further briefly maintain high levels of extra-cellular serotonin and dopamine in the NAC. However, moderate alcoholics or hyperphagics, with greater aminergic deficits, have to exaggerate normal hedonistic evening activities to maintain normal euphoric levels. The morbidly obese, bulimics,¹⁷ and severe alcoholics, unfortunately, have severely inadequate aminergic production in the NAC. They try to control their resulting dysphoria by eating or drinking excessively earlier in the day. Unable to stimulate aminergic production sufficiently, these descendants of Tantalus rarely reach satisfaction.

DESCRIPTION OF THE INVENTION

Described are therapeutic procedures and pharmaceutical compositions for attaining such therapy for treating a wide variety of apparently otherwise disparate conditions which may be generally termed addictive behaviors. These include alcoholism, dependence on drugs such as cocaine, crack cocaine, morphine, etc., but exclude the treatment of obese patients. Others benefiting from combined serotonin agonist(s) plus dopamine agonist(s) therapy include patients suffering from depression as well as manic depressive patients. I have observed significant reversal of depression within hours using the combination therapy rather than weeks and appears to be far more effective in selected patients than therapy with a single agent such as fluoxetine.

As a class, the serotonin agonists have been used to treat patients with addictive behaviors as have the dopamine agonists, both individually, and both with variable results. I have found that the concurrent use of a serotonin agonist and a dopamine agonist, preferably administered at the same time and desirably administered in the same dosage unit (tablet, capsule, solution),

provides highly effective, predictable therapy for patients suffering from forms of addictive behavior as illustrated below in the treatment of alcoholism.

In a preferred aspect of the invention the serotonin agonist(s) and dopamine agonist(s) are administered in the same unit dosage or pharmaceutical presentation. Current information indicates the use of a serotonergic drug reduces the potentially addictive qualities of dopaminergic drugs. Presentation in a single unit, desirably thoroughly blended together in a pharmaceutically stable combination, renders the potential for the separation of and possible abuse of the dopamine agonist far less likely. This aspect of the invention is particularly important in rendering the product administered unattractive to potential or current amphetamine addicts and thus reduces the potential for abuse.

Suitable formulations include those suitable for oral, rectal and parenteral (including subcutaneous, intradermal, intramuscular and intravenous) administration. The formulation may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy.

The oral route of administration is preferred, desirably in a single dosage unit. Therapeutic formulations suitable for oral administration in which the carrier is a solid are most preferably presented as unit dose formulations such as boluses, capsules or tablets each containing a predetermined amount of the active ingredients. A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredients in a free-flowing form such as a powder or granules

optionally mixed with a binder, lubricant, inert diluent, lubricating agent, surface-active agent or dispersing agent. Molded tablets may be made by molding active ingredients with an inert liquid diluent. Tablets may be optionally coated and, if uncoated, may optionally be scored. Capsules may be prepared by filling the active ingredients, either alone or in admixture with one or more accessory ingredients, into the capsule shells and then sealing them in the usual manner. Cachets are analogous to capsules in which the active ingredient together with any accessory ingredient(s) is sealed in a rice paper envelope.

Formulations of the invention also include dispersible granules, which may for example be suspended in water before administration, or sprinkled on food. The granules may be packaged, e.g. in a sachet. Formulations suitable for oral administration where the carrier is a liquid may be presented as a solution or a suspension in an aqueous liquid or a non-aqueous liquid, or as an oil-in-water liquid emulsion.

Formulations for oral administration include controlled release dosage forms, e.g. tablets where the active ingredients are formulated in an appropriate release - controlling matrix, or are coated with a suitable release - controlling film.

Therapeutic formulations suitable for rectal administration where the carrier is a solid are most preferably presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by admixture of the active ingredients with the softened or melted carrier(s) followed by chilling and shaping in molds.

Therapeutic formulations suitable for parenteral administration include sterile solutions or suspensions of the active ingredients in aqueous or oleaginous vehicles. Injectable preparations may be adapted for bolus injection or continuous infusion. Such preparations are conveniently presented in unit dose or multi-dose containers which are sealed after introduction of the formulation until required for use. Alternatively, the active ingredient may be in powder form which is constituted with a suitable vehicle, such as sterile, pyrogen-free water, before use.

Also contemplated are products formulated as long-acting depot preparations, which may be administered by intramuscular injection or by implantation, e.g. subcutaneously or intramuscularly. Depot preparations may include, for example, suitable polymeric or hydrophobic materials, or ion-exchange resins. Such long-acting formulations are particularly convenient for prophylactic use.

It should be understood that in addition to the above carrier ingredients the therapeutic formulations for the various routes of administration described above may include, as appropriate one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like, and substances included for the purpose of rendering the formulation isotonic with the blood of the intended recipient.

The compositions of the present invention may be administered in combination or concurrently with other therapeutic agents.

A wide variety of serotonin agonists and dopamine agonist may be considered for use in the therapeutic

methods and pharmaceutical compositions of the invention. The following is a non-limiting partial listing of products currently approved for use in the United States or other countries or in the final stages of regulatory approval.

1. Amphetamines -- At high doses cause release of dopamine from dopaminergic nerve terminals, particularly in the neostriatum. At still higher doses, cause release of 5-hydroxy-tryptamine (5-HT) and dopamine in the mesolimbic system.

Dextroamphetamine (Dexedrine®)
Methamphetamine (Desoxyn®)
Fenfluramine (Pondimin®)
Diethylpropion (Tenuate®)
Mazindol (Mazanor®)
Phentermine (Fastin®)
Benzphetamine (Didrex®)
Phendimetrazine (Phenazine®)
Phenmetrazine (Preludin®)
Chlorphentermine (Pre-Sate®)*
Clobenzorex*
Cloforex*
Methylphenidate (Ritalin®)
Pemoline (Cylert®)
Clortermine (Voranil®)*
Dexfenfluramine*
Ethylamphetamine*
Fenethylline*
Fenproporex*
Mefenorex*
Phenatine*
Phenbutrazate*
Prolintane*
Propylhexedrine*
Tiflorex*

2. Tricyclic antidepressants and other antidepressants -- block the reuptake of serotonin, dopamine, and/or norepinephrine at the neuronal membrane. The degree of potency and selectivity vary greatly among these agents.

Amitriptyline (Elavil®)
Amoxapine (Ascendin®)
Bupropion (Wellbutrin®)
Desipramine (Norpramin®)
Doxepin (Sinequan®)
Imipramine (Tofranil®)
Nortriptyline (Pamelor®)
Protriptyline (Vivactil®)
Trimipramine (Surmontil®)
Fluoxetine (Prozac®)
Sertraline (Zoloft®)
Paroxetine (Paxil®)
Trazodone (Desyrel®)
Clomipramine (Anafranil®)
Alaproctate*
Amineptine*
Butriptyline*
Cianopramine*
Citalopram*
Clovoxamine*
Dibenzepin*
Diclofensine*
Dimetacrine*
Dothiepin*
Femoxetine*
Fluvoxamine**
Iprindole*
Lofepramine*
Melitracen*
Minaprine*
Noxiptyline*
Opipramol*
Propizepine*

Quinupramine*

Viloxazine*

3. Monoamine Oxidase (MAO) Inhibitors -- block deamination of dopamine and serotonin.

Isocarboxazid (Marplan®)

Phenelzine (Nardil®)

Tranylcypromine (Parnate®)

Selegiline (Deprenyl®)

Clorgyline*

Iproclozide*

Iproniazid*

Mebanazine*

Moclobemide*

Nialamide*

Safrazine*

Toloxatone*

4. Dopamine Agonists -- immediate metabolic precursor of dopamine in the basal ganglia; or release of dopamine from central neurons in the basal ganglia (i.e., nigrostriatal neurons).

Levodopa/carbidopa (Sinemet®)

Amantadine (Symmetrel®)

Bromocriptine (Parlodel®)

Pergolide (Permax®)

Apomorphine

Benserazide*

Lysuride*

Mesulergine*

Lergotrile*

Memantine*

Metergoline*

Piribedil*

GBR12909* -- investigational

5. Miscellaneous

Buspirone (Buspar®) -- appears to act as a mixed agonist/antagonist at both the dopaminergic and serotonin receptors.

Lithium (Eskalith®) -- enhances the release of serotonin, especially in the hippocampus and may alter reuptake of catecholamines (i.e., dopamine).

Nicotine (Nicorette®, Habitrol® patch) -- stimulates release of norepinephrine and dopamine from brain tissue.

Phencyclidine -- inhibits reuptake of dopamine, serotonin, and norepinephrine by synapses.

Lysergic Acid -- serotonin agonist.

Reserpine (Ser-Ap-EsR) -- inhibit reuptake of dopamine and serotonin, resulting in depletion of stores.

Tryptophan -- a precursor of serotonin.

Oxitriptan* -- a precursor of serotonin.

In the above listing * indicates products not available in the United States and ** products to be marketed soon by Solvay Pharmaceuticals in the United States.

The preferred agents are fenfluramine and phentermine. Fenfluramine is a racemic mixture of a drug which releases serotonin to the central and peripheral nervous system and inhibits serotonin re-uptake into the neuron. Either optical isomer or a racemic mixture may be

used. Preferably the amount administered is from 10 to 90 mg/day in single or divided doses.

Phentermine is an adrenergic compound structurally related to amphetamines. Such agents typically increase dopamine and nor adrenaline concentrations at their respective receptor sites in the brain. Preferably the daily amount administered is 15 to 160 mg in single or divided doses.

For most treatments the above noted drugs are used in the dosage ranges and amounts indicated in the directions for use and labeling provided by the manufacturer of the product and/or stated in the relevant scientific literature. In particular, see the following sources Gilman et al. The Pharmacological Basis of Therapeutics, 7th ed. New York: Macmillan Publishing Co., 1985; McEvoy GK, ed. AHFS Drug Information, Bethesda, MD: American Society of Hospital Pharmacists, Inc., 1993; and Reynolds JE, ed. Martindale: The Extra Pharmacopoeia, 29th ed. London: The Pharmaceutical Press, 1989,

Phentermine and racemic fenfluramine treatment was given to twelve alcoholic patients. Eleven of twelve consecutive patients, most within hours, have noted a total loss or marked decrease in alcohol craving. Their consumption of alcohol has ceased or decreased markedly. This treatment is successful because of the dual and balanced increase in the bioavailability of the neurotransmitters dopamine and serotonin in the nucleus accumbens. Other addictive behaviors susceptible to such treatment with dual aminergic agonists may include cocaine, nicotine, narcotic and amphetamine addiction as well as depression and various presentations of obsessive compulsive behavior.

This invention is further explained with reference to the following non-limiting examples.

PREFERRED EMBODIMENTS OF THE INVENTION

Twelve heavy users of alcohol, testing the hypothesis that combining these same aminergic medications may also synergistically control alcoholism, were studied. The initial dose of fenfluramine was 80 milligrams daily; the starting dose of phentermine of 30 milligrams daily. In eleven of twelve consecutive patients there was a marked or total decrease in their alcoholic craving and consumption, usually in less than twenty-four hours.

Pharmaceutical presentation - capsules were prepared containing 80 mg. of fenfluramine hydrochloride and 30 mg. of phentermine hydrochloride powders distributed in a diluent of hydroxypropylmethyl cellulose (45 mg). The mixture was placed in a No. 1 capsule.

Representative case histories:

Ms A, a successful non-obese executive in her late twenties is the progeny of two alcoholics. In addition, there is a strong family history of depression, alcoholism and suicide. From the age of seven to seventeen her father abused her sexually. For at least the last ten years, Ms A has had a stormy alcoholic history. She reports that for years she had been binge drinking despite Alcoholics Anonymous meetings. Prior to the medication, Ms A suffered from ever present alcohol craving and obsessional ideation relieved only by alcohol. An in-patient on at least five occasions, her marriage is in dissolution. Her employers understandably, have wondered whether they can continue to employ her.

Ten weeks ago, the same evening she started the medication, she noted "absolutely no craving." Continuing to attend Alcoholics Anonymous meetings, she marvels at her voluntary alcoholic abstinence and lack of craving.

Prof. B, a college educator in his early fifties, came to the office several years ago for treatment of refractory hypertension. When questioned, he candidly discussed his alcohol history of more than one pint of vodka nightly. Up to the time of his interview, he asserted he had no insight into the possibility of alcoholism. He readily abstained from alcohol, lost thirty pounds and became normotensive. Over the last two years, he gained weight and once again had labile hypertension. He frankly commented that his alcohol craving had led to a resumption in drinking.

With the onset of the obesity program, he once again started to lose weight. The weight loss was not at the rate expected. However, when he increased his fenfluramine dose to 80 mg and lost his desire for alcohol his weight loss became precipitous. He has not consumed alcohol for ten weeks.

Mr. C, early sixties, started the medication eight weeks ago. He also has had complete loss of craving and is no longer drinking spirits. If he drinks at all, he limits it to a can or two of beer. He has started a support group which will help new people on the protocol.

Mrs. C, interviewed alone, clearly is very happy with the course. She states that he is a "new man," far more energetic and much less irritable.

REFERENCES

1. Litten RZ Allen J Pharmacotherapies for alcoholism: promising agents and clinical issues. *Alcohol Clin Exp Res* 1991 Aug;15(4):620-33
2. Sellers EM Higgins GA Tomkins DM Romach MK Toneatto T. Opportunities for treatment of psychoactive substance use disorders with serotonergic medications. *J Clin Psychiatry* 1991 Dec;52 Suppl:49-54.
3. Naranjo CA Kadlec KE Sanhueza P Woodley-Remus D Sellers EM. Fluoxetine differentially alters alcohol intake and other consummatory behaviors in problem drinkers. *Clin Pharmacol Ther* 1990 Apr;47(4):490-8
4. Naranjo CA Poulos CX Bremner KE Lanctot KL. Citalopram decreases desirability, liking, and consumption of alcohol in alcohol-dependent drinkers. *Clin Pharmacol Ther* 1992 Jun;51(6):729-39
5. Krasner N Moore MR Goldberg A Booth JC Frame AH McLaren AD. A trial of fenfluramine in the treatment of the chronic alcoholic patient. *Br J Psychiatry* 1976 Apr;128:346-53
6. Weintraub M Hasday JD Mushlin AI Lockwood DH. A double-blind clinical trial in weight control. Use of fenfluramine and phentermine alone and in combination. *Arch Intern Med* 1984 Jun;144(6):1143-8
7. Weintraub M Long-term weight control study: conclusions. *Clin Pharmacol Ther* 1992 May;51(5):642-6
8. Olds ME Yuwiler A: Effects of acute and chronic fenfluramine on self-stimulation and its facilitation by amphetamine. *Eur J Pharmacol* 1992 Jun 17;216(3):363-72

9. Holman RB Snape BM. Effects of ethanol in vitro and in vivo on the release of endogenous catecholamines from specific regions of rat brain. J Neurochem 1985 Feb;44(2):357-63

10. Yoshimoto K McBride WJ Lumeng L Li TK. Alcohol stimulates the release of dopamine and serotonin in the nucleus accumbens. Alcohol 1992 Jan-Feb;9(1):17-22

11. Alari L Lewander T Sjoquist B. The effect of ethanol on the brain catecholamine systems in female mice, rats, and guinea pigs. Alcohol Clin Exp Res 1987 Apr;11(2):144-9

12. Hoebel BG Hernandez L Schwartz DH Mark GP Hunter GA. Microdialysis studies of brain norepinephrine, serotonin, and dopamine release during ingestive behavior. Theoretical and clinical implications. Ann N Y Acad Sci 1989;575:171-91

13. Samson HH Tolliver GA Haraguchi M Hodge CW Alcohol self-administration: role of mesolimbic dopamine. Ann N Y Acad Sci 1992 Jun 28;654:242-53

14. Modell JG Mountz JM Beresford TP. Basal ganglia/limbic striatal and thalamocortical involvement in craving and loss of control in alcoholism. J Neuropsychiatry Clin Neurosci (1990 Spring) 2(2):123-44

15. Hobson JA Sleep New York: Scientific American Library 1989. 203 pp.

16. Hoebel BG Hernandez L Schwartz DH Mark GP Hunter GA. Microdialysis studies of brain norepinephrine, serotonin, and dopamine release during ingestive behavior. Theoretical and clinical implications. Ann N Y Acad Sci 1989;575:171-91; discussion 192-3

17. Leibowitz SF. The role of serotonin in eating disorders. Drugs (1990) 39 Suppl 3:33-48

WHAT IS CLAIMED IS:

1. A method of treating an addictive behavior, depression or manic depressive behavior, excluding obesity, comprising administering to a patient in need of same an effective amount of at least one serotonin agonist and at least one dopamine agonist wherein the combination of the serotonin agonist and the dopamine agonist are present in an amount effective to treat the patient's addictive behavior.
2. The method of claim 1 in which the addictive behavior is alcoholism.
3. The method of claim 1 in which depression is treated.
4. The method of claim 1 in which manic depressive behavior is treated.
5. The method of claim 1 in which the serotonin agonist and dopamine agonist are administered simultaneously.
6. The method of claim 5 in which the serotonin and agonist and dopamine agonist are intimately mixed together and administered in a single dosage unit.
7. The method of claim 1 in which the fenfluramine and pentermine are administered.
8. The method of claim 7 in which 10 to 90 mg of fenfluramine and 15 to 160 mg of pentermine are administered to the patient per day in single or divided doses.

9. A pharmaceutical composition for the treatment of addictive behaviors, depression or manic depressive behavior, excluding obesity, consisting essentially of, in combination, in a pharmaceutically acceptable carrier or diluent at least one serotonin agonist and at least one dopamine agonist, wherein the combination of the serotonin and the dopamine is present in an amount effective to treat said behavior.

10. The pharmaceutical composition of claim 9 in which the serotonin and dopamine are intimately blended together.

11. The pharmaceutical composition of claim 10 in which the serotonin agonist and dopamine agonist are contained in a single dosage unit.

12. The pharmaceutical composition of claim 11 as a tablet or capsule.

13. A pharmaceutical composition for the treatment of addictive behaviors, excluding obesity, consisting essentially in combination together with a pharmaceutically acceptable carrier or diluent, of from 15 to 160 mg of fenfluramine and from 10 to 90 mg of pentermine.

14. A tablet or capsule containing the pharmaceutical composition of claim 13.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US93/02875

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) : A61K 31/135
 US CL : 514/654, 810, 811, 910

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/654, 810, 811, 910

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, MEDLINE, BIOSIS, EMBASE, CAS-SEROTONIN, DOPAMINE, FENFLURAMINE, PHENTERMINE, ADDICTION, DEPRESSION, MANIA, BIPOLAR, OBESITY, ALCOHOLISM

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BIOSIS ABSTRACTS 9549752, ISSUED 1992, WEINTRÄUB ET AL., "LONG-TERM WEIGHT CONTROL STUDY...", SEE ABSTRACT NO. 94054752, CLIN PHARMACOL THER, 51(5), 586-594.	1-14
Y	US, A, 4,255,439 (COOPER) 10 MARCH 1981, SEE ENTIRE DOCUMENT.	1-14

Further documents are listed in the continuation of Box C. See patent family annex.

• Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be part of particular relevance		
E earlier document published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
O document referring to an oral disclosure, use, exhibition or other means	"&"	document member of the same patent family
P document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

13 JUNE 1994

Date of mailing of the international search report

JUN 24 1994

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

M. MOEZIE

Telephone No. (703) 308-1235